Mef2C is a lineage-restricted target of Scl/Tal1 and regulates megakaryopoiesis and B-cell homeostasis.

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Public Summary:
This work identified novel roles for transcription factor Mef2C in the blood system. We show that Mef2c has dual roles in regulating platelet production as well as protecting immune cells from premature aging.

Scientific Abstract:
The basic helix-loop-helix transcription factor stem cell leukemia gene (Scl) is a master regulator for hematopoiesis essential for hematopoietic specification and proper differentiation of the erythroid and megakaryocyte lineages. However, the critical downstream targets of Scl remain undefined. Here, we identified a novel Scl target gene, transcription factor myocyte enhancer factor 2 C (Mef2C) from Scl(fl/fl) fetal liver progenitor cell lines. Analysis of Mef2C(-/-) embryos showed that Mef2C, in contrast to Scl, is not essential for specification into primitive or definitive hematopoietic lineages. However, adult VavCre(+)Mef2C(fl/fl) mice exhibited platelet defects similar to those observed in Scl-deficient mice. The platelet counts were reduced, whereas platelet size was increased and the platelet shape and granularity were altered. Furthermore, megakaryopoiesis was severely impaired in vitro. Chromatin immunoprecipitation microarray hybridization analysis revealed that Mef2C is directly regulated by Scl in megakaryocytic cells, but not in erythroid cells. In addition, an Scl-independent requirement for Mef2C in B-lymphoid homeostasis was observed in Mef2C-deficient mice, characterized as severe age-dependent reduction of specific B-cell progenitor populations reminiscent of premature aging. In summary, this work identifies Mef2C as an integral member of hematopoietic transcription factors with distinct upstream regulatory mechanisms and functional requirements in megakaryocyte and B-lymphoid lineages.